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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/879,572 | 06/12/2001 | Arlene I. Ramsingh | 0189-2001 | 4742 |

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| EXAMINER | |
|---|---|
| CHEN, STACY BROWN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1648 | |

DATE MAILED: 01/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Applicati n No. | Applicant(s) | |
|---|---|---|---|
| | 09/879,572 | RAMSINGH ET AL. | |
| | Examin r | Art Unit | |
| | Stacy B Chen | 1648 | |

*-- The MAILING DATE of this communication appears on the c ver sh et with the corresp ndence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,6-15,17-28,30-36 and 54-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6-15,17,18,20-28 and 30-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *attached* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Applicant's response filed December 3, 2004 is acknowledged and entered. During telephonic interviews on January 12, 13, 14 and 18, 2005, Examiner Chen and Dr. Shmuel Livnat (Applicant's representative) attempted to reach agreement with respect to the claims, however, no agreement was reached. The substantive issues primarily discussed during the telephonic interviews are discussed in this Office action appear in paragraph numbers 3, 4 and 6. Prosecution in this application is reopened in view of further considerations. The Office regrets any inconvenience to Applicant. Claims 1, 3, 4, 6-15, 17-18, 20-28 and 30-36 are under examination. Claims 2, 19 and 54-72 are withdrawn from consideration as drawn to non-elected inventions.

2. The rejection of claims 1, 3, 4, 6-15, 17-18, 20-28 and 30-36 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for introducing new matter into the claims, is moot in view of Applicant's amendment which deleted the phrase in question ("non-coxsackievirus"). Applicant has presented arguments relating to the rejection, however, the rejection is now moot because of Applicant's amendment. Should Applicant amend the claims to recite the phrase in question, the arguments will be addressed.

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 4, 6-15, 17, 20-28 and 30-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. It is apparent that coxsackievirus CB4-P is required to practice the claimed invention because they are a necessary limitation for the success of the invention as stated in the claims. As a required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of coxsackievirus CB4-P. See 37 CFR 1.802. One cannot practice the claimed invention without the specifically named CB4-P coxsackievirus strain. Therefore, access to coxsackievirus CB4-P is required to practice the invention. While the specification provides a method for obtaining a virus that is like CB4-P, the specification does not provide a repeatable method for obtaining *the* CB4-P without access to *the* CB4-P and it does not appear to be readily available material.

Deposit of coxsackievirus CB4-P in a recognized deposit facility would satisfy the enablement requirements of 35 U.S.C. 112., because the strains would be readily available to the public to practice the invention claimed, see 37 CFR 1.801- 37 CFR 1.809.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 CFR 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of this application, access to the invention will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CFR 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition the identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803 - 37 CFR 1.809 for additional explanation of these requirements.

4. Claims 1, 3, 18 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant attenuated coxsackievirus B4 virion (or nucleic acid encoding said virion) which is engineered to contain a heterologous nucleic acid inserted within the P1 region of its genome, wherein the inserted nucleic acid encodes a heterologous polypeptide which is fused to a capsid protein of the virion, does not reasonably provide enablement for an insertion within any region of the open reading frame of its genome. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The breadth of the claims encompasses a recombinant virion (nucleic acid encoding said virion) wherein a heterologous nucleic acid is inserted within any part of the open reading frame of its genome. The nature of the invention is the insertion of heterologous nucleic acid encoding

a polypeptide into a coxsackievirus B4 genome to produce a fusion protein. The P1 region of the open reading frame contains all the structural proteins, whereas the P2 and P3 regions contain the non-structural proteins (specification, page 3, lines 19-23). In order for the heterologous nucleic acid to be expressed as a fusion protein with the capsid protein of the virion, the insertion would have to take place in the capsid region, namely, the P1 region (specification, page 6, lines 12-15). The state of the art shows that a coxsackievirus B4P (CB4-P) virion expressed a human immunodeficiency virus (HIV) p24 *gag* protein when inserted into the VP1 region of the CB4-P open reading frame (Halim *et al.*, *AIDS Research and Human Retroviruses*, 2000, 16(15):1551-1558, specifically page 1551, column 2, the full paragraph). The level of skill in the art is high, as evidenced by Halim *et al.*, as is the level of predictability regarding the placement of the insertion in order to have a fusion with the capsid protein. The amount of guidance and working examples in the specification with regard to the place of insertion of the heterologous nucleic acid are directed to the P1 region when desiring a fusion with the capsid protein (example 1). Given the breadth of the claims, the state of the art, the level of skill and predictability in the art and the guidance and working examples provided in the specification, the claims are only enabled for insertion in the P1 region in order to result in a fusion with the capsid protein of CB4. Therefore, claims 1, 3, 18 and 20-22 are not enabled for their full scope.

5. Claims 13-15 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to limitations of claim 1 and 18, respectively, wherein the insertion of nucleic acid is upstream of sequences which encode VP4,

and wherein the encoded heterologous polypeptide is expressed as an amino-terminal fusion of the viral polyprotein and subsequently cleaved off. It is unclear how the limitations in claims 13-15 and 28 relate with claims 1 and 18, which require that the encoded polypeptide be expressed as a fusion with the capsid protein which presumably remains fused to the capsid for display to antigen-presenting cells. Clarification and/or correction is required.

***Claim Rejections - 35 USC § 102***

6. Claims 1, 3, 4, 6-9, 18, 20-26, 31 and 33 are rejected under 35 U.S.C. 102(b) are anticipated by Caggana *et al.* (*J. Virol.*, 1993, 67:4797-4803, herein, "Caggana"). Previously, claims 1, 3, 4, 18 and 20-26 were rejected under 35 U.S.C. 102(b) as anticipated by Caggana, and subsequently the rejection was withdrawn. (The Second Declaration of Dr. Arlene Ramsingh was previously considered in the Office action dated June 3, 2004. The Second Declaration points to the differences between insertion and replacement technology. In view of these differences, the examiner withdrew the rejection.) However, upon further consideration, the rejection is now reinstated (with regard to claims 1, 3, 4, 18 and 20-26, previously rejected) because the claim *language* is emcompassed by an embodiment disclosed in Caggana. While the Office recognizes the difference between insertion versus replacement, the claim language, in its broadest reasonable interpretation, reads on various embodiments of "insertion". For example, an insertion (in its broadest sense) can be a deletion/insertion combination. Further, the meaning of the term "heterologous nucleic acid" in claims 1, 18 and all respective dependent claims, is interpreted in light of the specification. The specification defines the following terms on page 12, lines 28-33:

> "The term "heterologous polypeptide" refers to a polypeptide which is not otherwise naturally expressed by the virus. The term "heterologous nucleic acid" refers to any nucleic acid which is not otherwise naturally present in the genome of the virus at the position in which it is inserted."

In view of specification's broad definition, the prior art anticipates claims 1, 3, 4, 6-9, 18, 20-26, 31 and 33.

The claims are drawn to a recombinant attenuated coxsackievirus B4 virion which is engineered to contain a heterologous nucleic acid inserted within the open reading frame of its genome, which inserted nucleic acid encodes a heterologous polypeptide which is fused to a capsid protein of the virion. The recombinant attenuated coxsackievirus B4 virion (prior to insertion of nucleic acid) is a CB4-P virion. The insertion takes place in the P1 region (capsid region) of the genome, in particular the viral capsid region of VP1. The capsid region is an immunogenic region of the virion which comprises an epitope (B-cell and/or T-cell epitope). The heterologous polypeptide is situated within VP1 at a position which corresponds to the DE loop (see specification page 53), directly downstream of codon 129 of VP1 coding sequences. Also claimed are the nucleic acids encoding the recombinant attenuated coxsackievirus B4 virions with the inserts. The heterologous inserted nucleic acid encodes a T cell and/or B cell epitope. The heterologous inserted nucleic acid encodes a viral polypeptide or a fragment thereof.

Caggana teaches coxsackievirus CB4-P/CB4-V chimeras, in which an attenuated strain, CB4-P expresses heterologous CB4-V proteins of various types (P1, P2, P3) at various regions of the CB4-P genome, including just downstream from codon 129 of VP1, DE loop (page 4797-4798, "Construction of recombinant viruses"; page 4798, Figure 1; pages 4799-4801, bridging

paragraph; and page 4802, second column, first line). The VP1 region encodes capsid, which itself is immunogenic and thus contains epitopes (B-cell and/or T cell).

Applicant has argued that Caggana's chimerics are not intended to be encompassed by the instant claims because Caggana replaces regions of CB4 viruses with other regions of CB4 viruses. Applicant argues that the replacement of CB4-P genes with CV4-V genes is not a heterologous nucleic acid insertion. While the Office acknowledges that the CB4-P and CB4-V strains of coxsackievirus differ by about five amino acids, they remain structurally distinct strains because they have different amino acid sequences that renders one virulent and the other non-virulent. Even though the virulence is credited to one amino acid residue in the capsid protein of VP1 (Caggana, abstract), the sequences of the two remain different. The VP1 region of CB4-P is not the same as the VP1 region of CB4-V, structurally (amino acid difference) and functionally (virulent, non-virulent). As such, Caggana's chimeric meets the claim limitations of being a CB4 virion with heterologous nucleic acid inserted into an open reading frame that results in fusion to the capsid protein of the virion, wherein heterologous nucleic acid is defined as "not otherwise naturally present in the genome of the virus". In the instant case, the P1 region of CB4-V was not naturally present in the genome of the CB4-P virus. Therefore, the claims are encompassed by Caggana.

***Conclusion***

7. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

SBC
Stacy B. Chen
January 19, 2005

Approved
James C. Housel
1/24/05
JAMES HOUSEL
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